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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/568,153 | 02/13/2006 | Craig A. Coburn | 21504YP | 5916 |

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| EXAMINER | |
|---|---|
| JARRELL, NOBLE E | |

| ART UNIT | PAPER NUMBER |
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| 1609 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/568,153 | COBURN ET AL. | |
| | Examiner | Art Unit | |
| | Noble Jarrell | 1609 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,9-13 and 15-17* is/are rejected.

7)☒ Claim(s) *3,5-8,14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/13/2006 and 6/23/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application*

1. Claims 1-17 are pending in the application and are being examined in the current office action.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

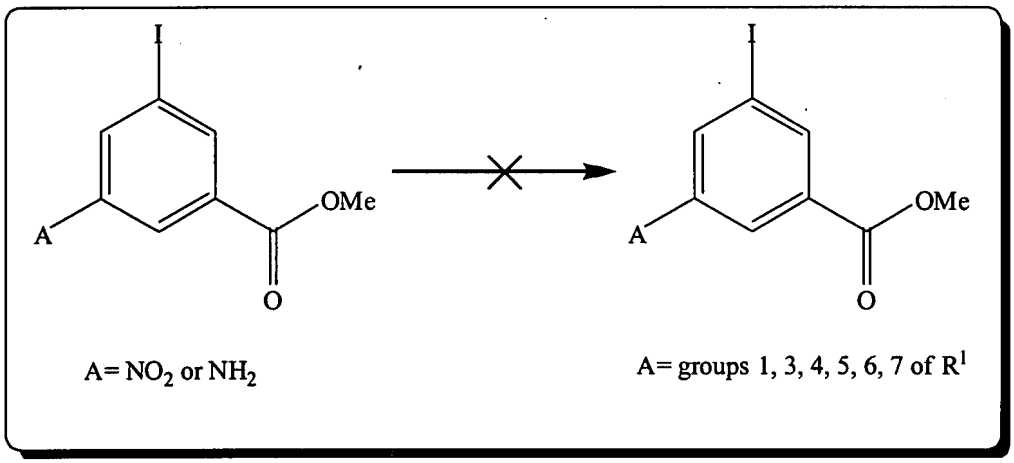
3. Claims 1, 2, 4, 9-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of formulae I-III wherein variable $R^1$ is $R^4$-$S(O)_pN(R^5)$- and for the method of using compounds of formula I-III wherein variable $R^1$ is $R^4$-$S(O)_pN(R^5)$-, does not reasonably provide enablement for situations where variable $R^1$ can be possibilities (1), (3), (4), (6), and (7). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Claims 15-17 are rejected under 35 USC 112, first paragraph, as lacking enablement.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The specification teaches the preparation of formulae I-III where variable $R^1$ is group 2 of variable $R^1$ in claim 1. This teaching is supported by Olah et al. (*Journal of Organic Chemistry*, 1993, 58,

3194-3195) because Olah et al. showed the proposed mechanism of the reaction and substrates in which the reaction will occur. They found that deactivated aromatics readily reacted with N-iodosuccinimide in the presence of triflic acid ($CF_3SO_3H$) to yield iodoarenes. The authors also found the reaction did not occur in the absence of triflic acid. It was also noted by Olah et al. that yields were very low or iodination did not take place at all when methylene chloride ($CH_2Cl_2$) was used as a solvent. One example shown in the table showed the conversion of nitrobenzene to 3-iodo-nitrobenzene in 86 % yield (page 3195, first entry in table I). The method of use cited in claims 16 is also enabled. The method of use is enabled because Coburn et al. (*Bioorganic and Medicinal Chemistry Letters,* **2006**,*16*, 3635-3638) found that a sulfonamide group occupies the $S_2$ binding pocket with the beta-secretase enzyme (page 3637, column 1, paragraph 4 to page 3638, column 1, paragraph 1). The sulfonamide oxygen forms hydrogen bonds with the enzyme. The following hydrogen bonds are formed: one with the NH of Asn233 and one with the OH of Ser235. In addition, the authors note that the amide bond is involved with two interactions that increase potency (Gln73 NH and Thr72 NH).

The specification does not teach synthetic scheme 1 (pages 9-10) when $R^1$ is not $R^4$-$S(O)_pN(R^5)$- nor does it teach the preparation of compound 2-A of scheme 2 (pages 11-12). In step A on page 19, the applicants react nitrobenzoate with N-iodosuccinimide in triflic acid to form the corresponding iodoarene. In step B, the nitro group is converted to an amine group by tin chloride. Then the amine is converted to a sulfonamide in step C. In claim 1, applicants claim 7 groups for variable $R^1$. However, applicants do not show support for the conversion of the nitroarene or the amino-arene to groups (1) and (3)-(7) of claim 1. The examiner did a search on this idea in STN CASReact and found no art that showed that one could convert a nitro or amine group to a hydrogen, cyano, $C_{1-6}$alkyl-CN, halogen, phenyl, or cycloalkyl-CN group.




Based on the search performed, 14 documents were retrieved but none of them showed the conversion of a nitro or amine group to groups (1) and (3)-(7) of variable $R^1$ in claim 1.

Claims 15-17 are not enabled because of the paper by Coburn et al. previously mentioned. These claims require that the compounds be pharmaceutically useful. The only groups that will effectively bind to beta-secretase are groups with amide bonds. Groups (1) and (3)-(7) do not contain amide bonds, so they cannot work as inhibitors of beta-secretase. Therefore, compounds of formulae I-III when variable $R^1$ is group (1) or (3)-(7) are not enabled as pharmaceutical agents as in claim 15 or for the method of use as cited in claims 16-17. Further, although beta-secretase is a desired enzyme to inhibit for the treatment of Alzheimer's Disease (Hull et al., *Drugs*, **2006**, *66(16)*, 2075-2093, page 2082, section 6.1), there have not been many studies of beta-secretase inhibitors. Hull et al. also state that beta-amyloid cleaving enzyme-1 (a beta-secretase) inhibitors are not easy to find because the enzyme has a large catalytic side that may not avidly bond with small molecules. Garino et al. (*Journal of Medicinal Chemistry*, **2006**, *49*, 4275-4285, lines 3-5 of the abstract) have done one of the first studies of beta-secretase inhibitors *in vitro*, but not *in vivo*. *In vitro* studies do not correlate to *in vivo* studies. The compounds tested by Garino et al. *may* work *in vivo*, but that event is not guaranteed because *in vivo* studies have not been performed. Therefore, claims 15-17 are not enabled.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

*(1) The nature of the invention and (2) the breadth of the claims:*

The claims are drawn to compounds of formulae I-III and their method of use. Thus, the claims taken together with the specification imply that Alzheimer's disease can be treated through the inhibition of beta-secretase.

*(3) The state of the prior art and (4) the predictability or unpredictability of the art:*

Examples 1-37 are free of the prior art. If variable $R^1$ is not group (2), it is undetermined if compounds of formulae I-III will function based upon Coburn et al. They state that peptide bond isosteres have worked as inhibitors (page 3635, column 2, paragraph 3), and based on this logic, groups (1) and (3)-(7) will not work. Group (6), even it can contain a carboxyl group, is controlled by a phenyl group which is much bigger than a carboxyl group.

*(5) The relative skill of those in the art:*

One of ordinary skill in the art is a synthetic chemist who is knowledgeable in the synthesis of macrocycles and the transformation of the nitro functional group.

*(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:*

The specification has provided guidance for preparing compound 1-A of scheme 1 when variable $R^1$ is group (2) of $R^1$ in claim 1. There is also guidance for the method of using this compound as an inhibitor of beta-secretase, and in turn, treating Alzheimer's disease.

However, the specification does not provide guidance for preparing compound 2-A of scheme 2 in the specification. There is no guidance for the preparation of this molecule, as compared to preparation of compound 1-A when variable $R^1$ is group (2) of variable $R^1$ in claim 1. Applicants state "Referring to scheme 2, phenol esters (2-A) (prepared as known in the art)...". However, no reference is provided for one to look at. There is no guidance for these molecules in the inhibition of beta-secretase.

*(8) The quantity of experimentation necessary*:

Considering the state of the art as discussed by the references above, particularly with regards to the preparation and the method of using the compounds and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims. Therefore, compounds 1-26 and 28-37 are enabled for their preparation and method of use. However, no other compounds are enabled.

***Claim Objections***

4. Claims 3, 5-8, and 14 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

5. The following is a statement of reasons for the indication of allowable subject matter: The closest reference is that of Coburn et al. (WO 2005018545 A2, published 3 March 2005). Examples 1-37 in the current specification on pages 19-28 are the same structures on pages 19-28 of WO 2005018545.

***Conclusions***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Noble Jarrell whose telephone number is (571) 272-9077. The examiner can normally be reached on Monday-Friday from 7:30 to 6:00. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-

direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NJ

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER